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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/445,328	12/07/1999	KUBER T. SAMPATH	JJJ-PO1-514	9813

28120 7590 05/15/2008

ROPES & GRAY LLP
PATENT DOCKETING 39/41
ONE INTERNATIONAL PLACE
BOSTON, MA 02110-2624

EXAMINER	
ROMEO, DAVID S	

ART UNIT	PAPER NUMBER
1647	

MAIL DATE	DELIVERY MODE
05/15/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/445,328	SAMPATH ET AL.	
	Examiner	Art Unit	
	David S. Romeo	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 February 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,5,6,8,9,11,12,14-38 and 53-65* is/are pending in the application.

4a) Of the above claim(s) *21,22,25 and 28-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,5,6,8,9,11,12,14-20,23,24,26,27,35-38 and 53-65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *2,5,6,8,9,11,12,14-38 and 53-65* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 02/04/2008 has been entered.

Claims 2, 5, 6, 8, 9, 11, 12, 14–38 and 53–65 are pending. Applicant's election with traverse of Group X, the species OP-1, the species the mature form of OP-1, the species pre-renal causes of acute renal failure, the species decreased cardiac output, and the species intravenous administration in the paper mailed 08/06/2002 is acknowledged. Claims 21, 22, 25 and 28-34 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention and/or species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the paper mailed 08/06/2002.

Applicant's election of GFR in the reply filed on 03/01/2005 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 2, 5, 6, 8, 9, 11, 12, 14-20, 23, 24, 26, 27, 35–38 and 53–65 are being examined only to the extent they read upon the elected invention and/or species.

Maintained formal matters, objections, and/or rejections:

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 2, 5, 6, 8, 9, 11, 12, 14, 23, 24, 26, 27, 35, 36, 37, 38, 53, 56 and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kelly (J Clin Invest. 1996 Feb 15;97(4):1056-63) in view of Kuberasampath (WO 93/04692) and Lefer (J Mol Cell Cardiol. 1992 Jun;24(6):585-93).

Kelly teaches that ICAM-1 is a key mediator of ischemic acute renal failure likely acting via potentiation of neutrophil-endothelial interactions (Abstract). Kelly shows an improvement of BUN and creatinine levels in ICAM-deficient mice after renal ischemia (page 1057, Figure 3). Kelly proposes that the protection afforded by knockout of the ICAM-1 gene is due to prevention of leukocyte accumulation in the kidney (page 1061, right column, full paragraph 1). The data of Kelly suggest that agents designed to block leukocyte-endothelial interactions mediated via ICAM-1 may be therapeutically effective in the prevention and treatment of acute renal failure (page 1062, left column, full paragraph 2). These data suggest a critical role for leukocytes and adhesion molecules, in particular ICAM-1, in the pathophysiology of ischemic acute renal failure and may have important therapeutic implications for the treatment of acute renal failure in

humans (page 1062, left column, full paragraph 3). Kelly does not teach administering OP-1 to a mammal afflicted with acute renal failure.

Kuberasampath teaches that damage to cells resulting from the effects of an inflammatory response by immune cell mediated tissue destruction has been implicated as the cause of reduced tissue function or loss of tissue function in the kidney (page 1, lines 21-33). Adhering neutrophilic leukocytes produce the humoral factors thought to mediate these damaging effects (page 2, full paragraph 1.) Kuberasampath provides a method for alleviating tissue damage associated with ischemic-reperfusion injury and for modulating the inflammatory responses in general. The method alleviates tissue damage associated with ischemic-reperfusion injury in a human which has suffered from hypoxia or ischemia following cardiac arrest, pulmonary embolus, renal artery occlusion, coronary occlusion or occlusive stroke. See page 7, line 10, through page 8, line 19.

Kuberasampath's method comprises the step of administering to the animal a therapeutically effective amount of a morphogenic protein upon tissue injury, or in anticipation of such injury, for a time and at a concentration sufficient to significantly inhibit or reduce the tissue destructive effects of the inflammatory response, including repairing damaged tissue, and/or inhibiting additional damage thereto (page 9, full paragraphs 1-2).

OP-1 is a morphogen that is useful in the method (page 14, full paragraph 1). Kuberasampath also teaches the mature form of human OP-1 (page 15, lines 1-2), which comprises amino acid residues 330-431 of human OP-1.

It is believed that the morphogens modulate the inflammatory response by modulating the attachment of immune effector cells to the luminal side of the endothelium of blood vessels at or near sites of tissue damage and/or inflammatory lesions. Kuberasampath's method not only relates to a method to reduce or prevent the immune cell-mediated cellular destruction at extravascular sites of recent tissue destruction, but also relates to a method to prevent or reduce the continued entry of immune effector cells into extravascular sites of ongoing inflammatory cascades. The morphogens are also contemplated for use in disrupting the functional interaction of immune effector cells with endothelium where the adhesion molecules are induced by means other than in response to tissue injury. See page 38, line 3, through page 40, line 9.

In addition to inhibiting the tissue destructive effects associated with the inflammatory response, the morphogens further enhance the viability of damaged tissue and/or organs by stimulating the regeneration of the damaged tissue (page 40, full paragraph 2).

The morphogen may be provided parenterally, such as by intravenous injection (page 51, lines 8-9). Typical dose ranges are given (paragraph bridging pages 59-60).

OP-1 (page 14, line 30, through page 15, line 17) inhibits the adherence of LTB4 activated PMNs to endothelium (Example 5, pages 74-75) and inhibits cellular and humoral inflammatory reactions (Example 7, pages 78-80).

Lefer teaches that hOP-1 exhibits significant anti-adherent actions on PMNs (page 592, left column, second sentence).

Kuberasampath and Lefer do not teach administering OP-1 to a mammal afflicted with acute renal failure (ARF). However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to administer an agent designed to block neutrophil-endothelial interactions to a mammal afflicted with ARF, as taught by Kelly, and to modify that teaching by administering OP-1, as taught by Kuberasampath and Lefer, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification because agents designed to block neutrophil-endothelial interactions may be therapeutically effective in the prevention and treatment of acute renal failure and OP-1 is an agent designed to block neutrophil-endothelial interactions.

BUN and creatinine levels improve in ICAM-deficient mice after renal ischemia (Kelly, page 1057, Figure 3). Therefore, one of ordinary skill in the art would have a reasonable expectation that administering OP-1 to a mammal afflicted with acute renal failure would improve BUN and creatine levels because (1) ICAM-deficient mice were protected from acute renal ischemic injury (Kelly, Abstract), (2) renal leukocyte infiltration was markedly less in ICAM-1-deficient than control mice (Kelly, Abstract), (3) neutrophil-depleted mice were also protected against ischemic renal failure (Kelly, Abstract), and (4) OP-1 is an agent designed to block neutrophil-endothelial interactions (Kuberasampath and Lefer). By definition, BUN and creatine levels are standard markers of kidney function (see claims 54 and 55). The instant specification also defines BUN or creatine as "a standard marker of renal function" (page 11, full paragraph 1). Furthermore, OP-1 further enhances the viability of damaged tissue and/or organs by stimulating the regeneration of the damaged tissue (Kuberasampath, page 40, full paragraph

2). Therefore, one of ordinary skill in the art would have a reasonable expectation of "effecting an improvement in a standard marker of renal function in the mammal afflicted with acute renal failure," as recited in claims 2 and 53.

The limitation "wherein said renal therapeutic agent: (a) induces chondrogenesis in an ectopic bone assay; or (b) prevents, inhibits, delays or alleviates loss of renal function resulting from acute renal failure in an animal of acute renal failure" (claims 2 and 53) only limits the properties of the agent administered and does not limit the claimed method. The OP-1 taught by Kuberasampath is identical to the OP-1 administered in the claimed method. Products of identical chemical composition can not have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, the properties of the agent administered that appellant discloses and/or claims are necessarily present in Kuberasampath's OP-1.

The invention is *prima facie* obvious over the prior art.

Response to Arguments

It is noted that on page 11 of the brief (Br.) applicants state that "[t]he examiner rejects claims 2, 53, and 58 as being allegedly obvious over Kelly…in view of Kuberasampath…and Lefer… ." This is not correct because:

(1) Claims 2 and 53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kelly in view of Kuberasampath and Lefer; and

(2) Claims 58, 61 and 64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kelly in view of Kuberasampath and Lefer as applied to claims 2 and 53 above, and further in view of Anderson and Brady.

As noted by applicants on page 10 of the Br., claims 2 and 53, unlike claim 58, are not limited to a pre-renal cause of cause acute renal failure. Thus, claims 2 and 53 are generic to claim 58. Therefore, if claim 58 is found unpatentable, then claims 2 and 53 would also be unpatentable. If claim 58 is found patentable, claims 2 and 53 are not necessarily patentable.

Applicants argue (Br., (1), page 12) that a reasonable expectation of success is lacking because the examiner has failed to show why one skilled in the art would have ignored the scientific literature documenting the adverse renal effects of anti-inflammatory agents, and why he would have selected the anti-inflammatory agent OP-1 to improve renal function in a subject with acute renal failure. In fact, one skilled in the art would have expected that the morphogen OP-1 would not only fail to improve renal function in a subject afflicted with acute renal failure, but also that it would aggravate the renal dysfunction. The skilled artisan would not have expected OP-1 to be the exception among anti-inflammatory agents.

Applicants' arguments have been fully considered but they are not persuasive. There is no evidence of record that OP-1 has any of the adverse renal effects of TGF-β, CsA or NSAIDs or that any of the adverse renal effects of TGF-β, CsA or NSAIDs are mediated through the blocking of neutrophil-endothelial interactions. Therefore, there is no evidence that a skilled artisan would have expected OP-1 to aggravate renal dysfunction. Therefore, the fact that TGF-β, CsA or NSAIDs may decrease renal function, or even to cause outright renal failure, is not a teaching away from using OP-1 to block neutrophil-endothelial interactions in a mammal afflicted with ARF. A skilled artisan would have selected OP-1 to improve renal function in a subject with acute renal failure because the data of Kelly suggest that agents designed to block leukocyte-endothelial interactions may be therapeutically effective in the prevention and

treatment of acute renal failure, and OP-1 blocks leukocyte-endothelial interactions, as taught by Kuberasampath and Lefer.

Applicants argue (Br., (2), page 12) that:

> Anti-inflammatory drugs were known to be detrimental to renal function. At the time the application was filed, it was well-documented in the scientific literature that anti-inflammatory agents reduced, rather than improved, renal function.
>
> On pages 10-16 of the Amendment filed on November 12, 2004, Applicants established that Transforming Growth Factor-β1 (TGF-β1), Cyclosporin A (CsA) and Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) were known at the time the subject application was filed to be both (i) anti-inflammatory agents which inhibit ICAM adhesiveness, and (ii) detrimental to renal function. The November 12, 2004 amendment included thirteen scientific publications, as Exhibits A-M, documenting the anti-inflammatory and the renal-adverse side effects of these three agents. Rather than reproducing this section of the previous office action in this appeal brief, Applicants provide a summary of the documented adverse renal effects of these three agents in Table B.

Applicants' arguments have been fully considered but they are not persuasive. The functional differences between OP-1 and TGF-β are well documented: For example,

> OP-1 promotes cell condensations and tubulogenesis in E11.5 metanephric mesenchyme, while TGF-β1 had no effect on metanephric differentiation under identical conditions. The growth of E11.5 cultures, as determined by DNA and protein content, was comparable to both OP-1 treated and untreated control, while TGF-β1 reduced the growth in E11.5 kidney cultures.

See Vukicevic (Proc Natl Acad Sci U S A. 1996 Aug 20;93(17):9021-6), page 9023, paragraph bridging left and right columns, and page 9024, paragraph bridging left and right columns.

> Direct comparison of TGF-β1 and hOP-1 in these bone cell cultures indicated that, although both hOP-1 and TGF-β1 promoted cell proliferation and collagen synthesis, only hOP-1 was effective in specifically stimulating markers of the osteoblast phenotype.

See Sampath (J Biol Chem. 1992 Oct 5;267(28):20352-62), Abstract.

> OP-1 induces both chondroblastic and osteoblastic differentiation of osteoprogenitor cells derived from newborn rat calvaria. TGF-β1 fails to induce

> any hypertrophic chondrocytes, and in combination with OP-1, TGF-β1 blocks OP-1-dependent chondroinduction.

See Asahina (J Cell Biol. 1993 Nov;123(4):921-33), Abstract. Therefore, the structural relatedness of OP-1 and TGF-β is not evidence of functional relatedness.

Regarding Exhibits D, F, I, K, L and M: Ketteler (Exhibit D), teaches that the fibrogenic effects of TGF-β in a rat model of acute renal injury model were shown to be due to three actions. First, TGF-β induced the synthesis of the extracellular matrix components that accumulate in glomerulosclerosis. Second, TGF-β decreased the action of the plasmin protease system, which is thought to be important in extracellular matrix turnover. Third, synthesis of β1 integrins, which play an important role in extracellular matrix assembly, was increased in the rat model. Interestingly, the addition of TGF-β to normal glomeruli in culture also increased the synthesis of matrix components, inhibited the plasmin protease system, and upregulated the expression of β1 integrins on the cells' surface. See page 447, right column, first full paragraph. The teachings of Exhibit F (Border. Curr Opin Nephrol Hypertens. 1994 Jan;3(1):54-8) are cumulative with those of Exhibit D with respect to the fibrogenic effects of TGF-β. However, there is no evidence of record that OP-1 possesses any of the fibrogenic effects of TGF-β1. In fact, Kuberasampath (WO 93/04692) recognizes that the morphogens, including OP-1, in contrast to fibrogenic growth factors such as TGF-β, stimulate tissue morphogenesis and do not stimulate fibrosis or scar tissue formation (page 40, last full paragraph; Example 9, pages 83-86), which is further evidence that TGF-β and OP-1 are functionally dissimilar. Therefore, the evidence (Exhibits D and F) that TGF-β is detrimental to renal function because excess TGF-β1

induces fibrogenesis, is not evidence that OP-1 is detrimental to renal function because OP-1 does not stimulate fibrosis or scar tissue formation.

Exhibit I (Wissmann et al. J Am Soc Nephrol. 1996 Dec;7(12):2677-81) indicates that the acute reduction in GFR (glomerular filtration rate) caused by Cyclosporine A is most likely the result of [renal] arteriolar vasoconstriction (Abstract). However, there is no evidence of record that OP-1 causes vasoconstriction or that a skilled artisan would expect OP-1 to act as a vasoconstrictor. It is worth noting that, acute cyclosporine-induced renal dysfunction is non-progressive, dose dependent, and reversed by dose reduction or discontinuation (Exhibit I, page 2677, right column, full paragraph 1). In other words, despite an acute reduction in GFR a skilled artisan would continue to use cyclosporine A for immunosuppression.

Exhibit K (Whelton et al. J Clin Pharmacol. 1991 Jul;31(7):588-98) discloses that prostaglandins are vasodilatory and maintain renal perfusion and function. The inhibitory effects of NSAIDs on renal prostaglandin production lead to acute, reversible renal failure in at-risk patients. (page 588, right column, last full paragraph). Many of the renal abnormalities that are encountered as a result of NSAID use can be attributed to the action of these drugs on prostaglandins (page 589, left column, full paragraph 3). The teachings of Exhibit L (Bennett et al. Am J Kidney Dis. 1996 Jul;28(1 Suppl 1):S56-62) are cumulative with those of Exhibit K with respect to the inhibitory effects of NSAIDs on renal prostaglandin production. The teachings of Exhibit M (Murray et al. Prog Drug Res. 1997;49:155-71, Abstract only) are cumulative with those of Exhibits K and L with respect to documenting the adverse renal side effects of NSAIDs in at-risk patients. However, there is no evidence of record that a skilled

artisan would expect OP-1 to act as a vasoconstrictor, or that OP-1 inhibits renal prostaglandin production.

There is no evidence of record that inhibition of neutrophil adherence by OP-1 would cause any of the renal side-effects associated with the use of TGF-β1, CsA, or NSAIDs. Therefore, the argument that a skilled artisan would not expect that OP-1 could be used to treat acute renal failure because some agents that have antiinflammatory effects also have adverse renal effects cannot rebut the *prima facie* case of obviousness.

Applicants argue (Br., (3), page 13) that:

> One skilled in the art would have expected that administration of OP-1 to a mammal afflicted with acute renal failure would reduce, not increase, renal function.
>
> OP-1 shares two key properties with TGF-β1, CsA and NSAIDs: (i) it decreases ICAM adhesiveness and (ii) it decreases PMC activity. OP-1 and TGF-β1 are also members of the TGF-β superfamily of growth factors. The Examiner has focused exclusively on OP-l's anti-inflammatory property as the key attribute in making it a seemingly successful candidate for treating Acute Renal Failure (ARF).
>
> But at the time the application was filed, anti-inflammatory agents were documented to actually cause renal dysfunction, especially in subjects with already impaired renal function. One skilled in the art would have expected that OP-1, just like its counterpart anti-inflammatory agents TGF-β1, CsA and NSAIDs, would further impair renal function in a subject afflicted with acute renal failure. One skilled in the art would have expected that administration of the anti-inflammatory OP-1 polypeptide, based on its anti-inflammatory and neutrophil adhesion- inhibiting properties that it shares with NSAIDs, would reduce, rather than increase, renal function. If anything, the documented anti-renal effects of anti-inflammatory agents taught away from administering anti-inflammatory agents, such as OP-1, to subjects with impaired renal function.
>
> While having the burden of proof, the Examiner has failed to establish why one skilled in the art would have made OP-1 the exception amongst anti-inflammatory agents. He has failed to show why one would have expected OP-1 to be the anomaly and to actually improve renal function where other anti-inflammatory agents failed. The burden of going forward was and is on the Examiner to

> overcome the presumption of lack of reasonable expectation of success legitimately established by applicant using documentary evidence during prosecution. Because he has failed to do so, he has failed to establish a prima facie case of obviousness in accordance with MPEP 706.02(j).

Applicants' arguments have been fully considered but they are not persuasive. The examiner believes that he has already addressed these arguments in response to applicants' arguments at (1) and (2) of the brief, as discussed above. Briefly,

- The structural relatedness of OP-1 and TGF-β is not evidence of functional relatedness;
- OP-1, in contrast to fibrogenic growth factors such as TGF-β, stimulates tissue morphogenesis and does not stimulate fibrosis or scar tissue formation.. Therefore, evidence that excess TGF-β1 induces fibrogenesis, which is detrimental to renal function, is not evidence that OP-1 is detrimental to renal function;
- There is no evidence of record that OP-1 causes vasoconstriction, that a skilled artisan would expect OP-1 to act as a vasoconstrictor, or that OP-1 inhibits renal prostaglandin production; and
- There is no evidence of record that inhibition of neutrophil adhesiveness causes any of the renal side-effects of TGF-β1, CsA, or NSAIDs.
- Therefore, the argument that a skilled artisan would not expect that OP-1 could be used to treat acute renal failure because some agents that have antiinflammatory effects also have adverse renal effects is mere argument and cannot rebut the *prima facie* case of obviousness and reasonable expectation of success.

Applicants argue (Br., (4), page 14) that:

> The examiner's counterarguments fail to address why OP-1 would have been expected to be the exception among anti-inflammatory agents.
>
> …the burden is on the Examiner, not on applicants, to establish the third prong of the prima facie case of obviousness. It is the Examiner who must who must present evidence why one skilled on the art would have expected a fourth anti-inflammatory agent (OP-1) to be the exception among anti-inflammatories – to show why a fourth anti- inflammatory would be effective in treating acute renal failure when the three others anti-inflammatory agents impair renal function. The

> Examiner wants Applicants to provide evidence that OP-1 had the adverse renal effects of the other anti-inflammatory agents. But this is impossible because Applicants discovered that, contrary to expectation, OP-1 could improve renal function.
>
> (i) The Examiner's position turns the test for obviousness on its head because the standard is the reasonable expectation that the invention would work successfully, and not whether there was the infinitesimal chance that OP-1 might improve renal function contrary to expectation. Since there is no evidence supplied by the Examiner that OP-1 would be effective in treating ARF, and documentary evidence shows that other anti-inflammatories were ineffective, there is no prima facie case of obviousness.
>
> (ii) The question is not whether the possibility exists, no matter how small, that two compounds can have different properties. The question is what properties one skilled in the art would have expected the morphogens to have and why one would have expected OP-1 to be an exception. The claimed invention runs counter to conventional wisdom.
>
> (iii) The Examiner seeks to prematurely shift the burden of proof to Applicants, when the Examiner's own initial burden of proof has not yet been satisfied.

Applicants' arguments have been fully considered but they are not persuasive. To the extent that applicants are arguing that the antiinflammatory agents TGF-β, CsA and NSAIDs have adverse renal effects and would not be used to treat acute renal failure, and therefore one of ordinary skill in the art would not use OP-1 to treat renal failure, the examiner believes that he has already addressed these arguments in response to applicants' arguments at (1) and (2) of the brief.

Furthermore, one of ordinary skill in the art would have a reasonable expectation of success because OP-1 inhibits neutrophil-endothelial interactions, as taught by Kuberasampath and Lefer, and because agents designed to block neutrophil-endothelial interactions may be therapeutically effective in the prevention and treatment of acute renal failure, as taught by Kelly. The examiner does not rely on some standard of "exception" or "anomaly" in order to make the

prima facie case. The examiner believes that he has established a *prima facie* case of reasonable expectation of success and obviousness that applicants have failed to rebut.

Claim Rejections - 35 USC § 103

Claims 2, 15-20, 53, 54, 55 and 58–65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kelly (J Clin Invest. 1996 Feb 15;97(4):1056-63) in view of Kuberasampath (WO 93/04692) and Lefer (J Mol Cell Cardiol. 1992 Jun;24(6):585-93) as applied to claims 2 and 53 above, and further in view of Anderson (Chapter 275, in Harrison's Principles Of Internal Medicine, 1980) and Brady (Chapter 236, in Harrison's Principles Of Internal Medicine, 1994).

Kelly in view of Kuberasampath and Lefer teach administering OP-1 to a mammal afflicted with acute renal failure, as discussed above. Kelly in view of Kuberasampath and Lefer are silent with respect to the acute renal failure being one arising from a pre-renal cause of acute renal failure (claims 58, 61 and 64), administering the agent continuously during the period of acute renal failure, wherein the period of acute renal failure lasts from one to three weeks (claim 61), and a mammal afflicted with acute renal failure wherein the mammal is afflicted with osteodystrophy (claim 64).

Anderson teaches that impaired cardiac output is a major cause of acute deterioration in renal function (page 1293, Table 275-1).

Brady teaches that low cardiac output is one of the major causes of prerenal acute renal failure (page 1266, Table 236-1). Severe or prolonged hypoperfusion may lead to intrinsic renal azotemia (page 1266, left column, full paragraph 1). Management of acute renal failure should focus on elimination of the causative hemodynamic abnormality or toxin, avoidance of

additional insults, and prevention and treatment of complications (page 1272, right column, full paragraph 3).

Anderson and Brady do not teach administering OP-1 to a mammal afflicted with acute renal failure. However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to administer OP-1 to mammal afflicted with acute renal failure, as taught by Kelly in view of Kuberasampath and Lefer, and to modify that teaching by administering OP-1 to a mammal afflicted with acute renal failure arising from a pre-renal cause of acute renal failure, as recited in claims 58, 61 and 64, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification because impaired cardiac output is a major cause of acute deterioration in renal function one of the major causes of prerenal acute renal failure (Anderson, page 1293, Table 275-1), and the management of acute renal failure should focus, in part, on avoidance of additional insults and prevention and treatment of complications (Brady, page 1272, right column, full paragraph 3). One would expect kidney tissue destructive effects from the inflammatory response that ensues from the deprivation of oxygen to the kidney during impaired cardiac output (Kuberasampath, page 7, line 10, through page 8, line 19), and one would expect OP-1 to inhibit the tissue destructive effects associated with the inflammatory response and further enhance the viability of damaged tissue and/or organs by stimulating the regeneration of the damaged tissue, according to the teachings of Kuberasampath (page 40, full paragraph 2).

Insofar as Kelly in view of Kuberasampath and Lefer and further in view of Anderson and Brady teach the treatment of acute renal failure in a mammal afflicted with a pre-renal cause of acute renal failure by administering OP-1, then administering the agent continuously during

the period of acute renal failure, wherein the period of acute renal failure lasts from one to three weeks, as recited in claim 61, would have been obvious absent any evidence that this difference is unexpected, unobvious, or critical. This difference is obvious because one of ordinary skill in the art would be motivated to avoid additional kidney tissue insults, such as the tissue destructive effects of an inflammatory response, as much as possible and for as long as possible in order to preserve or restore kidney function as much as possible. Furthermore, Kuberasampath teaches administering a therapeutically effective amount of a morphogenic protein upon tissue injury, or in anticipation of such injury, for a time and at a concentration sufficient to significantly inhibit or reduce the tissue destructive effects of the inflammatory response, including repairing damaged tissue, and/or inhibiting additional damage thereto (page 9, full paragraphs 1-2). Therefore, the determination of the length of treatment is well within the purview of an ordinarily skilled artisan.

Insofar as the prior art teaches the prevention and treatment of acute renal failure by administering OP-1, then the differences between the teachings of the references relied upon and the limitations of claims 60–65 would have been obvious absent any evidence that these differences are unexpected and unobvious. Further with respect to claim 63, it is noted that Brady teaches that a rise in serum creatine of greater than 3 mg/dL is associated with a poor prognosis and probably reflects the extent of renal parenchymal damage and severity of the underlying disease (page 1274, paragraph bridging left and right columns). These differences are obvious because one of ordinary skill in the art would be motivated to treat and prevent the acute renal failure.

Further with respect to claim 64, the specification discloses:

> That is, the subjects for treatment are expected to be otherwise free of indications for morphogen treatment. In some number of cases, however, the subjects may present with other symptoms (e.g., osteodystrophy) for which morphogen treatment would be indicated. Paragraph bridging pages 11-12.

The examiner uses the specification as dictionary for a definition of subjects for treatment. Kelly in view of Kuberasampath and Lefer and further in view of Anderson and Brady do not teach a mammal afflicted with osteodystrophy. However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to administer OP-1 to a mammal afflicted with acute renal failure, the acute renal failure being one arising from a pre-renal cause of acute renal failure, as taught by Kelly in view of Kuberasampath and Lefer and further in view of Anderson and Brady, and to modify this teaching by administering OP-1 to a mammal afflicted with acute renal failure, the acute renal failure being one arising from a pre-renal cause of acute renal failure, wherein the mammal is afflicted with osteodystrophy, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification because one of ordinary skill in the art would be motivated to treat the acute renal failure.

The invention is *prima facie* obvious over the prior art.

Response to Arguments

Applicants argue (Br., (4)(i)-(iii), page 15) that:

> The Examiner's position turns the test for obviousness on its head. …there is no evidence supplied by the Examiner that OP-1 would be effective in treating ARF, and documentary evidence shows that other anti- inflammatories were ineffective, there is no prima facie case of obviousness.
>
> …The question, however, is not whether the possibility exists, no matter how small, that two compounds can have different properties. The question is what

> properties one skilled in the art would have expected the morphogens to have and why one would have expected OP-1 to be an exception. Merely pointing out that OP-1 is a different compound than TGF-β1, CsA or an NSAID, proves nothing. TGF-β1, CsA or an NSAID all have different structures from each other yet they all reduce inflammation and reduce renal function. The common teaching of such prior art is that anti-inflammatories generally have an adverse effect on renal function. The claimed invention runs counter to conventional wisdom.
>
> The Examiner seeks to prematurely shift the burden of proof to Applicants, when the Examiner's own initial burden of proof has not yet been satisfied. Specifically, the Examiner is requiring applicants to prove that OP-1 would not be expected to exhibit the harmful renal effects of other anti-inflammatory agents, when it is the Examiner who bears the initial burden of showing why OP-1 should be considered as the exception amongst anti-inflammatory agents. MPEP 2142 imposes the initial burden on the examiner, and this burden has not been meet.

Applicants' arguments have been fully considered but they are not persuasive. By definition, BUN and creatine levels are standard markers of kidney function (see claims 54 and 55). The instant specification also defines BUN or creatine as "a standard marker of renal function" (page 11, full paragraph 1). BUN and creatinine levels improve in ICAM-deficient mice after renal ischemia (Kelly, page 1057, Figure 3). Kelly proposes that the protection afforded by knockout of the ICAM-1 gene is due to prevention of leukocyte accumulation in the kidney (page 1061, right column, full paragraph 1). ICAM-1 is a key mediator of ischemic acute renal failure likely acting via potentiation of neutrophil-endothelial interactions (Kelly, Abstract). The data of Kelly suggest that agents designed to block leukocyte-endothelial interactions mediated via ICAM-1 may be therapeutically effective in the prevention and treatment of acute renal failure (page 1062, left column, full paragraph 2).

One of ordinary skill in the art would have a reasonable expectation that administering OP-1 to a mammal afflicted with acute renal failure would improve BUN and creatine levels because (1) ICAM-deficient mice were protected from acute renal ischemic injury (Kelly,

Abstract), (2) renal leukocyte infiltration was markedly less in ICAM-1-deficient than control mice (Kelly, Abstract), (3) neutrophil-depleted mice were also protected against ischemic renal failure (Kelly, Abstract), and (4) OP-1 is an agent designed to block neutrophil-endothelial interactions (Kuberasampath and Lefer). Furthermore, OP-1 further enhances the viability of damaged tissue and/or organs by stimulating the regeneration of the damaged tissue (Kuberasampath, page 40, full paragraph 2). Therefore, one of ordinary skill in the art would have a reasonable expectation of "effecting an improvement in a standard marker of renal function in the mammal afflicted with acute renal failure," as recited in claims 2, 53, 58, 61 and 64.

Furthermore, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to administer OP-1 to mammal afflicted with acute renal failure, as taught by Kelly in view of Kuberasampath and Lefer, and to modify that teaching by administering OP-1 to a mammal afflicted with acute renal failure arising from a pre-renal cause of acute renal failure, as recited in claim 58, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification because impaired cardiac output is a major cause of acute deterioration in renal function one of the major causes of prerenal acute renal failure (Anderson, (page 1293, Table 275-1). The management of acute renal failure should focus, in part, on avoidance of additional insults and prevention and treatment of complications (Brady, page 1272, right column, full paragraph 3). One would expect kidney tissue destructive effects of the inflammatory response that ensues from the deprivation of oxygen to the kidney during impaired cardiac output (Kuberasampath, page 7, line 10, through page 8, line 19), and one would also expect OP-1 to inhibit the tissue destructive effects associated with the

inflammatory response and further enhance the viability of damaged tissue and/or organs by stimulating the regeneration of the damaged tissue, according to the teachings of Kuberasampath (page 40, full paragraph 2).

The examiner concludes that a *prima facie* case of obviousness has been established. The examiner also concludes that applicants' "documentary evidence" (Exhibits D, F, I, K, L and M) does not rebut the *prima facie* case of obviousness for the reasons discussed above. Briefly,

- The structural relatedness of OP-1 and TGF-β is not evidence of functional relatedness;
- OP-1, in contrast to fibrogenic growth factors such as TGF-β, stimulates tissue morphogenesis and does not stimulate fibrosis or scar tissue formation.. Therefore, evidence that excess TGF-β1 induces fibrogenesis, which is detrimental to renal function, is not evidence that OP-1 is detrimental to renal function;
- Unlike CsA and NSAIDS, there is no evidence of record that OP-1 causes vasoconstriction, that a skilled artisan would expect OP-1 to act as a vasoconstrictor, or that OP-1 inhibits renal prostaglandin production; and
- There is no evidence of record that inhibition of neutrophil adhesiveness causes any of the renal side-effects of TGF-β1, CsA, or NSAIDs.

With respect to claim 61, Applicants argue (Br., page 16) that:

> … the failure to establish a reasonable expectation of success for the method of claim 58 also applies to the method of claim 61, thus rendering claim 61 nonobvious.
>
> A failure to establish a prima facie case of obviousness for claim 61 also arises from the failure of the Examiner to establish a basis as to how the combination of cited references teaches or suggests all the elements of claim 61. In particular, the Examiner has not shown how the combination of cited references allegedly teaches (i) the treatment of a period of acute renal failure lasting from only one to three weeks; and (ii) the continuous administration of OP-1 during this one to three week period of acute renal failure.
>
> …The Examiner must specifically point out how all the elements of claim 61, are allegedly taught by the combination of references, must point out how the

> references could be combined to achieve the claimed method, and must point out why one skilled in the art would have had a reasonable expectation of success in treating acute renal failure by administering the morphogen only during a period of one to three weeks. Since the Examiner has failed to show meet these three burdens, a prima facie case of obviousness has not been made.

Applicants' arguments have been fully considered but they are not persuasive. The examiner believes that he has established a *prima facie* case of reasonable expectation of success and obviousness for claim 58 and that applicants have failed to rebut this *prima facie* case, as discussed above.

Furthermore, the test for obviousness is not whether the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). As indicated above, administering OP-1 continuously during the period of acute renal failure, wherein the period of acute renal failure lasts from one to three weeks, would have been obvious absent any evidence that this difference is unexpected, unobvious, or critical. This difference is obvious because one of ordinary skill in the art would be motivated to avoid additional kidney tissue insults, such as the tissue destructive effects of an inflammatory response, as much as possible and for as long as possible in order to preserve or restore kidney function as much as possible. Furthermore, Kuberasampath teaches administering a therapeutically effective amount of a morphogenic protein upon tissue injury, or in anticipation of such injury, for a time and at a concentration sufficient to significantly inhibit or reduce the tissue destructive effects of the inflammatory response, including repairing damaged tissue, and/or inhibiting additional damage thereto (page 9, full paragraphs 1-2).

Therefore, the determination of the length of treatment is well within the purview of an ordinarily skilled artisan.

With respect to claim 64, Applicants argue (Br., page 17) that:

> … the failure to establish a reasonable expectation of success for the method of claim 58 also applies to the method of claim 64, rendering claim 64 also nonobvious.
>
> A failure to establish a prima facie case of obviousness also arises from the failure of the Examiner to establish a basis as to how the combination of cited references teaches or suggests the treatment of a subject afflicted with osteodystrophy as recited in claim 64.
>
> The Examiner has not identified any teachings or suggestions in the combination of cited references for treating subjects who are additionally afflicted with osteodystrophy. Instead, the Examiner impermissibly tries to use the specification itself as one of the 103(a) references. The Examiner claims to use "the specification as a dictionary for [the] definition of subjects for treatment" (page 3, lines 20-21 of the Office Action dated September 21, 2006), and concludes that it would have been obvious to treat a subject afflicted with osteodystrophy.
>
> But it is the combination of cited reference, and not the specification of the subject application, that must teach or suggest all the claim elements. This section of the specification states that "[i]n some number of cases, however, the subjects may present with other symptoms (e.g. osteodystrophy) for which morphogen treatment would be indicated." (page 12, lines 5-6). The Examiner cannot use the specification as a reference against itself. The suggestion or teaching to treat subjects afflicted with osteodystrophy must be found in the prior art. And the section of the specification cited by the Examiner is not providing any type of definition. It is showing embodiments of subjects that may be treated with OP-1.
>
> The Examiner has failed to meet his burden of establishing why treatment of ARF patients additionally afflicted with osteodystrophy is allegedly taught by the prior art, and therefore has failed to make a prima facie case of obviousness under MPEP § 706.020).

Applicants' arguments have been fully considered but they are not persuasive. The examiner believes that he has established a *prima facie* case of reasonable expectation of success

and obviousness for claim 58 and that applicants have failed to rebut this *prima facie* case, as discussed above.

Furthermore, the test for obviousness is not whether the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). The difference between claims 58 and 64 would have been obvious to one of ordinary skill in the art because it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to administer OP-1 to a mammal afflicted with acute renal failure, wherein the mammal is afflicted with osteodystrophy, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification because one of ordinary skill in the art would be motivated to treat the acute renal failure.

The examiner believes that he has correctly used the specification as a dictionary in order to merely to understand what applicants have claimed. The paragraph bridging pages 11-12 establishes the non-criticality of the "osteodystrophy" limitation.

Conclusion

No claims are allowable.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114.

See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

ANY INQUIRY CONCERNING THIS COMMUNICATION OR EARLIER COMMUNICATIONS FROM THE EXAMINER SHOULD BE DIRECTED TO DAVID S. ROMEO WHOSE TELEPHONE NUMBER IS (571) 272-0890. THE EXAMINER CAN NORMALLY BE REACHED ON MONDAY THROUGH FRIDAY FROM 9:00 A.M. TO 5:30 P.M. IF ATTEMPTS TO REACH THE EXAMINER BY TELEPHONE ARE UNSUCCESSFUL, THE EXAMINER'S SUPERVISOR, MANJUNATH RAO, CAN BE REACHED AT (571)272-0939.

IF SUBMITTING OFFICIAL CORRESPONDENCE BY FAX, APPLICANTS ARE ENCOURAGED TO SUBMIT OFFICIAL CORRESPONDENCE TO THE CENTRAL FAX NUMBER FOR OFFICIAL CORRESPONDENCE, WHICH IS (571) 273-8300.

CUSTOMERS ARE ALSO ADVISED TO USE CERTIFICATE OF FACSIMILE PROCEDURES WHEN SUBMITTING A REPLY TO A NON-FINAL OR FINAL OFFICE ACTION BY FACSIMILE (SEE 37 CFR 1.6 AND 1.8).

ANY INQUIRY OF A GENERAL NATURE OR RELATING TO THE STATUS OF THIS APPLICATION OR PROCEEDING MAY BE OBTAINED FROM THE PATENT APPLICATION INFORMATION RETRIEVAL (PAIR) SYSTEM. STATUS INFORMATION FOR PUBLISHED APPLICATIONS MAY BE OBTAINED FROM EITHER PRIVATE PAIR OR PUBLIC PAIR. STATUS INFORMATION FOR UNPUBLISHED APPLICATIONS IS AVAILABLE THROUGH PRIVATE PAIR ONLY. FOR MORE INFORMATION ABOUT THE PAIR SYSTEM, SEE HTTP://PAIR-DIRECT.USPTO.GOV. CONTACT THE ELECTRONIC BUSINESS CENTER (EBC) AT 866-217-9197 (TOLL-FREE) FOR QUESTIONS ON ACCESS TO THE PRIVATE PAIR SYSTEM,

/DAVID ROMEO/
PRIMARY EXAMINER
ART UNIT 1647

DSR
MAY 8, 2008